PATENT COOPERATION TREATY

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REC'D 19 OCT 2005
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 150386/KB	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/CZ2004/000067	International filing date *(day/month/year)* 14.10.2004	Priority date *(day/month/year)* 17.10.2003
International Patent Classification (IPC) or national classification and IPC A61K9/20, A61K31/00, A61K9/16		
Applicant PLIVA-LACHEMA A.S.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.07.2005	18.10.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Luangkhot, N Telephone No. +49 89 2399-7857

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CZ2004/000067

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-8	as originally filed

Claims, Numbers

6-11	as originally filed
1-5	received on 08.06.2005 with letter of 06.06.2005

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2
	No:	Claims	1,3-10
Inventive step (IS)	Yes:	Claims	2
	No:	Claims	1,3-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item I

Basis of the report

1) The documents cited in the International Search Report (ISR) were numbered respectively from D1-D5; this numbering results from the citation order in the ISR and will be used for the procedure. **Unless otherwise specified, the cited passages of each document in the ISR will be considered.**

D1: CHAUDRY I A ET AL: "MIGRATION OF POTENT DRUGS IN WET GRANULATIONS" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 61, no. 7, 1972, pages 1121-1125, XP009045712 ISSN: 0022-3549

D2: WO 91/04031 A (E.I. DU PONT DE NEMOURS AND COMPANY) 4 April 1991 (1991-04-04)

D3: WO 01/60338 A (ALPHARMA APS; LYNENSKJOLD, EVA; JOERGENSEN, LONE, NOERGAARD) 23 August 2001 (2001-08-23)

D4: WO 03/037379 A (DEGUSSA AG) 8 May 2003 (2003-05-08)

D5: AMANN A H: "Effect of formulation on dissolution of sodium warfarin tablets" JOURNAL OF PHARMACEUTICAL SCIENCES 1973, vol. 62, no. 9, 1973, pages 1573-1574, XP009045711

2) Amendments

Amended claim 1, which excludes the "one excipient case", is allowable according to Article 34(2)(b) PCT because it restores novelty over D3 and D4 by delimiting the claim against an accidental anticipation. In D3 and D4, warfarin is cited among a long list of possible active substances. Nowhere in D3 and D4 is any mention regarding either the problem of content uniformity or a teaching suggesting how said problem could be solved.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3) Subject-matter of present application

The subject-matter of present application is directed to a method of producing dosage units of warfarin sodium salt having a high degree of content uniformity.
The technical solution provided in claim 1 consists in **bringing in** contact an aqueous solution of warfarin sodium salt with solid particles of at least two excipients.
The technical solution provided in claim 2 consists in **spraying** the said aqueous solution onto solid particles of at least two excipients.

4) Novelty and inventive step

4a) D1 is directed to a method of improving the content uniformity of sodium warfarin tablets prepared by a wet granulation. D1 solves a migration of a highly water soluble sodium warfarin occurring during post-granulation drying by using excipients being able to act as migration inhibitors such as calcium phosphate. Prior to the granulation step, the warfarin sodium is in form of a **powder blend** in D1 (see p.1123 col.1 §1), whereas in present application it is in form of an **aqueous solution**. Thus the solution provided by D1 is different from the process of the present application, which is therefore novel and inventive over D1.

4b) D2-D4 are not relevant to present application with respect to novelty and inventive step. They do not mention present process, nor the problem of content uniformity of warfarin, nor a teaching for solving the said problem.

4c) D5 describes a process for preparing warfarin granules wherein warfarin sodium is dissolved in an aqueous solution, then **"poured"** onto a powder mixture of microcrystalline cellulose-lactose (see Table I, p.1573 col.2 L.10-12 and 30).
D5 deals with the problem of dissolution rate of warfarin which is affected by the excipients used.

As the starting products and the manufacturing process in claim 1 are **identical** (in claim 1: the solution is brought in contact; in D5: the solution is poured), then the obtained products of D5 and of present application **are identical** in all other respects, that is to say the particles of D5 have **implicitly and inevitably** a high degree of

content uniformity meeting the Bergum criterion, even if D5 does not mention it.

In such a case an objection as to lack of novelty arises in the first place and **the burden is on the Applicant to provide evidence** for the novelty of the claimed method. Such evidence should be of a technical character (for instance experimental data or conclusive arguments). The mere statement that the solid dosage forms of D5 do not fulfil the Bergum criterion is not sufficient (see also guidelines **C-IV, 7.5.**).

If the applicant is able to show, e.g. by **appropriate comparison tests**, that differences do exist with respect to the friability parameter, it is questionable whether the independent claim discloses **all the features essential to manufacture products having parameters specified in the claims** (Art. 5 and 6 PCT).

Having said that, the subject-matter of **claim 1 is not novel** in view of D5. However the subject-matter of **claim 2 is novel** since D5 does not say that the aqueous solution of warfarin is brought in contact by **spraying**.

The technical solution provided in claim 2, which consists in spraying an aqueous solution of warfarin sodium salt onto solid particles of at least two excipients, is inventive over D5 because this latter does not mention the problem of content uniformity of warfarin, nor a teaching for solving the said problem. Furthermore the applicant shows on page 8 Table 2 that the problem is solved using the process of claim 2.

For the regional phase:

Re Item VII

Certain defects in the international application

5) Contrary to the requirements of Rule 5.1(a)(ii) PCT, it seems that the relevant background art disclosed in the documents D1 and D5 is not mentioned in the description, nor are these documents identified therein.

6) Any information the applicant may wish to submit concerning the subject-matter of

the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application.

7) The attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). Preferably these indications should be submitted in handwritten form on a copy of the relevant parts of the application as filed.

CLAIMS

1. The method of producing dosage units of a solid drug form containing as the active substance warfarin sodium salt in an amount of 1 to 10 mg and having high degree of content uniformity meeting Bergum criterion, characterized in that a required amount of an aqueous solution of warfarin sodium salt and/or its clathrate which optionally contains in the dissolved state one of pharmaceutically acceptable excipients co-forming the solid drug form to be prepared but not all the pharmaceutically acceptable excipients co-forming the solid drug form to be prepared, is brought into contact with solid particles of at least two pharmaceutically acceptable excipients co-forming the solid drug form to be prepared, whereupon optionally the particles are dried and optionally mixed with the required amount of solid particles of the remaining pharmaceutically acceptable excipients co-forming the solid drug form to be prepared, and the thus-obtained particulate mixture is formulated into dosage units of the solid drug form.

2. The method according to claim 1, characterized in that the bringing into contact of an aqueous solution of warfarin sodium salt and/or its clathrate with solid particles of at least one pharmaceutically acceptable excipient is performed by spraying this solution onto these solid particles.

3. The method according to claim 1 or 2, characterized in that the aqueous solution of warfarin sodium salt and/or its clathrate contains 1 to 50 % by weight, preferably 8 to 35 % by weight, of warfarin sodium salt and/or its clathrate, based on the weight of the solution.

4. The method according to any of claims 1 to 3, characterized in that the aqueous solution of warfarin sodium salt and/or its clathrate contains, beside water, solely warfarin sodium salt and/or its clathrate.

5. The method according to any of claims 1 to 4, characterized in that the solid particles of at least one pharmaceutically acceptable excipient intended for bringing into contact with aqueous solution of warfarin sodium salt and/or its clathrate, have such particle distribution that the size of at least 90 % of these particles is greater than 40 micrometers, the size of at most 10 % of these particles is greater than 250 micrometers, and 100 % of these particles are of a size not exceeding 300 micrometers.